REMARKS

Claims 1, 2, 4-12, 14, 15, 28, 30-36, 43 and 47-54 are pending in the application. Claims 1 and 15 are currently amended, and claims 47-54 are new claims.

The specification is amended in response to Examiner's objection to the inconsistent statements in the previous version of specification. No new matter is present in the specification as amended.

Specification Objections

The specification is objected to for multiple reasons. Applicants have amended the specification to overcome the objections.

(A) The specification is objected to because the disclosure for the structure of the AviIII polypeptide is unclear. Applicants have amended the specification so that the delineation of the domain structure is consistent with the structure represented in Figure 1 as originally filed.

(i) The specification on page 5, paragraph 5 has been amended by deleting reference to CBD_II and FN_III domains.

(ii) The specification on page 16, paragraph 4 to page 17, paragraph 1 has been amended so that the numbering of amino acids is consistent with SEQ ID NO. 1.

(iii) The inconsistency is resolved by the amendment in (ii) above.

(iv) The inconsistency is resolved by the amendment in (ii) above.

(B) Examiner objected to the specification because the phrase "substrate targeting moiety" is unclear. The specification on page 14 has been amended to clarify that "Substrate targeting moiety" refers to any signal on a substrate, or any signal on other molecules (or ligand) bound to such a substrate, used to target any AviIII polypeptide or fragment thereof to a substrate. Applicants believe that the amendment should render the definition of "Substrate targeting moiety" clear and unambiguous.

Claims Objections

Applicants would like to bring to Examiner's attention that Claim 1 was amended in Applicants' response to Office Action dated June 16, 2004 by replacing AviIII_Aace with AviIII_Aac. Claim 15 is currently amended by deleting the extra colon.

Claim Rejections—35 U.S.C. 112 second paragraph

Claims 1, 2, 4-11, 14 and 15 are rejected under 35 U.S.C. §112 second paragraph as being indefinite. Examiner asserted that the claims fail to "provide any structural or functional limitations or definition of the polypeptide encompassed." Applicants traverse for the reasons stated below.

Claims 1, 2, 4-11, 14 and 15 define the claimed polypeptide as having a primary structure of with certain degree of identity to SEQ ID NO. 1. It is unclear what better types of limitations Examiner has in mind that would provide better definition of the claimed composition than the structural limitation based on the primary sequence in the instant application. Definition of polypeptides based on sequence identity is commonly used by scientists to classify different families of

proteins, and retention of functionality is on the basis of 90% sequence identity. Such claims are well defined and withdrawal of the 35 U.S.C. §112 second paragraph rejections is respectfully requested.

Examiner also rejected Claims 1, 2, 4-11, 14 and 15 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Examiner stated that the specification fails to define the structure of both the GH74 and the CBD III domains. Applicants have amended the specification to resolve some inconsistencies in the specification. The specification as amended, clearly points out the structure of the GH74 domain as shown both in SEQ ID NO. 1 and SEQ ID NO. 3. Similarly, the structure of the CBD III domain is now well defined by the text of the specification, Table 2 and Fig. 1. Withdrawal of the rejection based on 35 U.S.C. §112 second paragraph is respectfully requested.

Examiner further rejected Claim 32 under 35 U.S.C. §112 second paragraph for reciting "substrate targeting moiety." The Examiner also asserts that the term "substrate" is not defined in the specification. Applicants traverse this assertion. On page 9, last paragraph of the currently amended specification, "substrate" is defined as "a polymer such as cellulose or can be a complex molecule or aggregate of molecules where the entire moiety comprises at least some cellulose." Withdrawal of the rejection based on 35 U.S.C. §112 second paragraph is respectfully requested.

Claim Rejections—35 U.S.C. §112 first paragraph—Enablement

Claims 1, 2, 4-12, 14, 15, 28, 30-36 and 43 are rejected under 35 U.S.C. §112 first paragraph for lack of enablement. The Examiner asserts that the recitation of the limitation of specific residues to be conserved in the polypeptide of SEQ ID NO. 1 constitutes new matter and that the specification fails to provides sufficient enablement for the claimed invention. Applicants respectfully disagree for reasons explained below.

The Examiner will appreciate that the replication of Table 5 as formerly presented in claim 1 has been moved to claims 47 and 50. Thus, the objection is moot with respect to claim 1 and the associated dependant claims. The conservation of specific residues is taught in the specification by Table 5 and discussion of the conserved sequence among cellulases of the same family in Example 2. The specification is also replete with discussion of site-directed mutagenesis and other methodology of making amino acid changes. See pages 21-23. It is hardly a new concept at the time the present application was filed that changes in conserved residues are more likely to result in alterations in protein structure and/or function. Therefore, the limitation of substitution of conserved residues recited in the Claims is not new matter.

Applicants acknowledge that further experiments are required for making the residue substitutions. However, the full sequence comparison to homologous proteins provides reasonable guidance for such experimentation, so that such experimentation is not undue. Site-directed mutagenesis is standard technique for determining which residues in a protein are essential for folding or function. *See* DeGrado *et al.*, Protein Design, a Minimalist Approach, *Science*, 1989,

243:622-28. Given appropriate motivation, those skilled in the art would be able to follow the guidance provided by the present invention to generate variants of AviIII using standard techniques in the field. Therefore, the disclosure of the full sequence and its alignment with homologous enzymes enables one of ordinary skill in the art to practice the claimed invention, i.e., variants of the AviIII enzyme that share substantial sequence similarity with the native enzyme or its domains thereof.

Examiner also cited Guo et al. to show the tremendous number of possibilities for residue substitutions. Guo et al. is exploring protein tolerance to random substitutions. The instant specification teaches the importance of conserving some amino acids as evidenced by sequence similarity between AviIII of Acidothermus and Avicelase III of Aspergillus. Claim 1 and its dependent claims, as amended, also recite the limitations of thermal tolerability and cellulase activity. Thus, the polypeptides claimed are clearly defined by both structure and function. Withdrawal of rejections for lack of enablement under 35 U.S.C. §112 first paragraph is respectfully requested.

Claim Rejections—35 U.S.C. §112 first paragraph--written description

Claims 1, 2, 4-11, 14, 15, 28, 30-36 and 43 stand rejected under 35 U.S.C. §112 first paragraph for insufficient written description. Examiner asserted that the recitation of the limitation of specific residues to be identical to SEQ ID NO. 3 constitutes new matter and that the specification fails to describe the functions for the full scope of the claimed polypeptides. Applicants respectfully disagree for reasons set forth below.

As explained in the previous section under "Enablement," the conservation of specific residues is taught in the specification by Table 5 and discussion of the conserved sequence among cellulases of the same family in Example 2. The sequence used for the alignment in Table 5 is SEQ ID NO. 3. The specification is also replete of discussion for making residue changes in a protein. Therefore, the limitation of residues of the catalytic domain identical to the polypeptide of SEQ ID NO. 3 is not new matter.

Examiner stated that Applicants fail to describe the functions for the full scope of the claimed polypeptides. Claim 1 and its dependent claims, as amended, recite the limitations of thermal tolerability and cellulase activity. Thus, the polypeptides claimed are clearly defined by both structure and function.

Examiner further rejected Claims 10 and 11 under 35 U.S.C. §112 first paragraph for introducing new matter by reciting 80% or 90% sequence identity to SEQ ID NO. 3. The specification provides "[t]he amino acid sequence of AviIII polypeptides of the invention is preferably at least about 60% identical, more preferably at least about 70% identical, or in some embodiments at least about 90% identical, to the AviIII amino acid sequence shown above in Table 3 and SEQ ID NO:1." See page 20, last paragraph. Although SEQ ID NO: 3 is not mentioned in this sentence, Table 1 shows that SEQ ID NO: 3 is a part of SEQ ID NO:1. One skilled in the art would appreciate that SEQ ID NO:1 encompasses SEQ ID NO: 3 and that sequences that share identity to SEQ ID NO:1 would similarly share sequence identity to SEQ ID NO: 3. Withdrawal of rejections for insufficient

written description under 35 U.S.C. §112 first paragraph is respectfully requested.

Claim Rejections—35 U.S.C. §102

Claims 1, 2, 4-12, 14, 15, 28, 36 and 43 stand rejected under 35 U.S.C. §102(b) as being anticipated by Adney et al., 1994 or Tucker et al. 1989. The rejection postulates an unwarranted assumption that the cellulases in Adney et al., 1994 or Tucker et al. 1989 are identical to AviIII of the present invention. Tucker 1989 and Example 7 of Adney 1994 each reports an enzyme having a molecular weight of from 156,000 to 203,400 daltons, which possesses C1 and Cx types of enzymatic activity. The Examiner observes that the deduced molecular weight of the claimed AviIII cellulase based upon SEQ ID NO. 1 is approximately 105 kDa, which is smaller than the size of the high molecular weight cellulase disclosed by Tucker 1989 and Adney 1994, but larger than the low molecular weight cellulase disclosed by Tucker 1989 and Adney 1994. The Examiner therefore assumes that the claimed cellulase is the same as the high molecular weight cellulase reported by Tucker 1989 and Adney 1994, with glycosylation accounting for the weight discrepancy. We respectfully traverse that finding on the basis that the applied reference is speculative and relies only on the Examiner's assumption.

What the Examiner assumes as a basis for the speculative presumption is simply untrue. AviIII cannot be the same high molecular weight cellulase taught by Tucker 1989 and Adney 1994. While glycosylation of secreted extracellular enzymes is common among eukaryotes, *Acidothermus* and most other bacteria

do not glycosylate secreted proteins. Therefore, the 105 kDa Avicellase of this application cannot be the endoglucanase(s) taught by Tucker 1989 or Adney 1994 on the basis of molecular weight alone.

The declaration submitted with Applicants' response to an Office Action dated August 1, 2002 provides additional facts that deserve consideration and are relevant to the §102 rejection, as well as the §103 rejection below. The Declaration contains additional statements regarding the inability of *Acidothermus* to glycosylate cellulases. The Declaration also provides additional information regarding the serendipitous discovery of AviIII, which was discovered as a xyloglucanase gene attached to an endoglucanase fragment when screening for endoglucanases. AviIII-derived cellulases cannot be the high molecular weight composition identified as an endoglucanase in Tucker 1989 and Adney 1994, as indicated by the xyloglucanase versus endoglucanase distinction. Withdrawal of the rejection under 35 U.S.C. 102(b) is respectfully requested.

Claim Rejections—35 U.S.C. §103

Claims 1, 2, 4-12, 14, 15 and 28 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Mohaghegi et al. 1986 in view of 'Berghem et al. 1976 and Katz et al. 1968. Mohaghegi et al. 1986 is said to show the isolation of *Acidothermus cellulolyticus*, but not the isolation of cellulase therefrom. Berghem et al. 1976 is used to show the isolation of an endoglucanase from *Trichoderma viride*. Katz et al. supposedly shows motivation to combine, since it is desirable to generate alternative cellulases capable of commercial scale processing at

elevated temperatures. We respectfully traverse because the Office has not shown a *prima facie* case of obviousness.

"To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *See* MPEP 2143.03. At present, no reference teaches or suggests the GH74 family polypeptide that is claimed. This is an *exoglucanase* or modified exoglucanase, for example, as shown in SEQ ID NO. 1. In contrast, Mohaghegi et al. 1986 in view of Berghem et al. 1976 and Katz et al. 1968 uses Berghem et al. to show the isolation of a cellulase, but the cellulase is an *endoglucanase*. Therefore, this cannot be the GH74 family polypeptide that is claimed. As Paragraph 9 of the Rule 132 Declaration filed December 26, 2002 makes clear, the claimed GH74 domain functions as an exoglucanase, not an endoglucanase. It follows that the combination does not teach or suggest all of the claim limitations because the combination, if proper, would merely result in the isolation of an endoglucanase from *A. celllulolyticus*. Therefore, Mohaghegi et al. 1986 in view of Berghem et al. 1976 and Katz et al. 1968 does not teach the isolation of an *exoglucanase*.

Furthermore, in order to establish a prima facie case of obviousness, the references must provide sufficient guidance and enabling methodology for practicing the claimed invention with reasonable expectation of success. Examiner has acknowledged in the Office Action dated June 16, 2004 that Claim 1 of the application recites "substantially purified AviIII peptide," and that a protein preparation would not be deemed purified for the purpose of the present invention if the preparation contains more than about 10% of contaminating

substances. There is no indication that Berghem et al. has achieved this level of purity.

In fact, Berghem teaches the purification up to a point when the peaks for 280 nm absorbance and avicelase activity coincide (See e.g., Fig. 6). However, as is well known in the field, contaminating proteins sometimes co-purify with the target protein. In other words, contaminating proteins that possess no avicelase activity may be present under the same 280 nm absorbance peak in the same fraction as the target enzyme. Therefore, just because the peaks for 280 nm absorbance and avicelase activity coincide does not mean that Berghem has achieved a purity of more than 90%. Without a showing of purity commensurate with that of the present invention, the three references, taken as a whole, do not provide enabling methodology with reasonable expectation of success to motivate one of ordinary skill to attempt to prepare the exoglucanase of the present invention to a purity of about 90%. Applicants respectfully request withdrawal of the 35 U.S.C. §103 rejections.

The Examiner on page 124 of the present office action clarifies that the Berghem reference is not cited to show purification of the claimed exoglucanse, rather, Berghem is cited to show methods that would or might be useful in purifying an exoglucanase. We fail to understand this use of Berghem because we are claiming a composition, not a method. This use of Berghem is inapposite to 35 U.S.C. §103(a), which says "[p]atentability shall not be negatived by the manner in which the invention was made." The Examiner relies upon Berghem—a reference that used methodology resulting in the purification of an

endoglucanase, not an e*xoglucanase*. If anything, Berghem teaches away from the composition that is claimed because a purified endoglucanase should have resulted from this methodology.

The Commissioner is authorized to charge any additionally required fees to deposit account 14-0460. Should the Examiner have any questions, comments, or suggestions that would expedite the prosecution of the present case to allowance, Applicants' representative, Paul White, earnestly requests a telephone call at (303) 384-7575.

Respectfully submitted

Paul J. White, Reg. No. 30,436
Attorney for Applicants

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National Renewable Energy Laboratory
1617 Cole Blvd.
Golden, CO 80401
303/384-7575
303/384/7499 (Fax)